Vaccines for healthcare associated infections without vaccine prevention to date

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ABSTRACT

In spite of the widespread implementation of preventive strategies, the prevalence of healthcare-associated infections (HAIs) remains high. The prevalence of multidrug resistant organisms is high in HAIs. In 2019, the World Health Organization retained antimicrobial resistance as one of the ten issues for global health. The development of vaccines may contribute to the fight against antimicrobial resistance to reduce the burden of HAIs. *Staphylococcus aureus*, Gram negative bacteria and *Clostridium difficile* are the most frequent pathogens reported in HAIs. Consequently, the development of vaccines against these pathogens is crucial. At this stage, the goal of obtaining effective vaccines against *S.aureus* and Gram negative bacteria has not yet been achieved. However, we can expect in the near future availability of a vaccine against *C. difficile*. In addition, identifying populations who may benefit from these vaccines is complex, as at-risk patients are not great responders to vaccines, or as vaccination may occur too late, when they are already confronted to the risk. Vaccinating healthcare workers (HCWs) against these pathogens may have an impact only if HCWs play a role in the transmission and in the pathogens acquisition in patients, if the vaccine is effective to reduce pathogens carriage and if vaccine coverage is sufficient to protect patients. Acceptance of these potential vaccines should be evaluated and addressed in patients and in HCWs.

Introduction

The global burden of healthcare-associated infections (HAIs) [1,2] results in tremendous financial costs [3,4]. In spite of the implementation of infection control strategies, HAIs prevalence remains high, ranging between 4 and 10% in acute care settings in Europe and in the United States of America [1,5,6]. In France, a study conducted in 2017 including more than 80,000 patients found an estimated prevalence of HAIs of 5.21% [1]. Urinary tract infections, surgical site infections (SSI), pneumonia and bacteremia were the major affected sites in France [1]. In the USA, pneumonia, SSI and gastrointestinal infections were the major sites of HAIs [7]. Among patients with microbiologically documented HAIs, *Escherichia coli (E.coli)*, *Staphylococcus aureus (S. aureus)*, *Enterococcus faecalis (E. faecalis),* and *Pseudomonas aeruginosa (P. aeruginosa)* were the most frequent pathogens isolated in France [1]. In the USA, *Clostridium difficile* was responsible for 12.1% of the HAIs [7]. In Asia, most HAIs were related to *P. aeruginosa, Klebsiella species (K. spp)* and *Acinetobacter baumannii (A. baumannii)* [8].

While infection control measures play a crucial role in the prevention of HAIs and the limitation of the diffusion of the involved organisms, they are not sufficient to stem the burden of HAIs [9]. Moreover, HAIs are associated with a high prevalence of multidrug resistant organisms (MDRO) [10,11]. In the WHO European Region in 2020, third generation cephalosporin resistant *E. coli* and *K. pneumoniae* accounted for more than 50% of the isolates in 13% and 44% of the countries respectively [12]. Imipenem resistant *A. baumannii* accounted for more than 50% of the isolates in 55% of the European Countries [12]. Many of key factors contributing to the development and spread of antimicrobial resistance are concentrated in healthcare settings (immunocompromised patient

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populations, a large number of indwelling devices, and widespread use of broad spectrum antibiotics...). To illustrate, in 2015 the prevalence of antimicrobial use in the USA in acute care was estimated to be at 49.5% [6].

Thus, the management of these MDRO related infections represents a challenge in the era of antimicrobial resistance threats [13]. Indeed, antimicrobial resistance was identified in 2019 as one of the ten threats on the public health by the World Health Organization (WHO) [14]. The limits of antimicrobial drugs for the treatment of MDRO infections have in part been reached already and deaths directly due to the lack of therapeutic options for treatment of totally-drug resistant organisms infections have been reported [15]. More broadly, mortality associated with MDRO infections (either directly-one due to the resistance or indirectly-one due to the comorbidities of the patients infected) have been estimated to reach up to 12,500 deaths a year in France [16] and 35,000 deaths a year in the USA [17]. In the European Union, in 2018, the European Center of for Diseases Prevention and Control had estimated that MDRO causes 33,000 deaths a year [18]. Parallel to the increase in antimicrobial resistance, the development of new antimicrobials is rare [19] and thus alternative strategies are urgently needed to prevent and treat HAIs.

Among these strategies, vaccines and passive immunization are probably of the most attractive ones to decrease the overall burden of bacterial disease and the associated need for antibiotics in the context of HAIs [19]. Moreover, vaccines might be a mean to fight antibiotic resistance, as was observed after the implementation of the vaccine against *Streptococcus pneumoniae* in the general population [20]. For more than a decade, immunological approaches to reduce HAIs have been considered [21]. However, vaccine development for HAIs, has been hampered by a poor understanding of correlates of protection and the lack of predictive animal models *e.g* for *S. aureus* vaccine [22].

In this narrative review, we focus on in-development vaccines that are or could be used to prevent bacterial HAIs and to reduce the burden of antimicrobial resistance. For this review, we first identified last epidemiological data about HAI in Europe, and in the USA. We searched on PUBMED and clinicaltrials.gov for advances in vaccine clinical development against most frequent HAIs bacterial pathogens since the publication of a previous published narrative review [23]. For each pathogen, we used [the name of the pathogens] and [vaccine] as keywords. Accurate articles cited in selected articles were also read and integrated in the reference if they bring additional information.

Overview of potential vaccines against bacterial and fungal healthcare-associated infections

In 2017, the WHO published a list of bacteria for which new antibiotics were urgently needed, classifying pathogens on their antimicrobial resistance level [24]. In addition to new antimicrobials, vaccines might contribute to reduce the burden of diseases due to these pathogens, different reviews or reports brought a general overview [25,26]. To illustrate this article, Table 1 depicted the 10 more frequent pathogens responsible for HAI in France. Vaccines reached clinical development for 6 of these pathogens.

Staphylococcus aureus vaccines

S. aureus is a human commensal organism and also a pathogen. Approximately 30% of the general population are colonized by *S. aureus* [27]. In parallel, this bacterium can cause different types of infections, ranging from noninvasive skin and soft tissue infections to bacteremia, endocarditis and osteomyelitis [28]. *S. aureus* is one of the leading causes of HAIs, notably involved in devices-

Table 1
The 10 more frequent pathogens responsible for HAI in France and existence of corresponding vaccines in clinical development from Enquête nationale de prévalence des infections nosocomiales et des traitements anti-infectieux en établissements de santé, France, mai-juin 2017. Santé Publique France 2018 [11].

Pathogens	Percentage of HAI in France	Vaccine in clinical development	WHO priority list
Escherichia.coli	23.6	Yes	Critical
Staphylococcus aureus	13.8	Yes	High
Enterococcus faecalis	6.5	No	
Pseudomonas aeruginosa	6.3	Yes	Critical
Klebsiella pneumoniae	5.6	Yes	Critical
Staphylococcus epidermidis	5.4	No	
Enterobacter cloacae	3.8	No	Critical
Proteus mirabilis	2.9	No	Critical
Clostridium difficile	2.3	Yes	
Candida albicans	1.5	Yes	
Enterococcus faecium	1.5	No	High

related infections [5,7,11]. This pathogen also harbors resistance to antibiotics and methicillin resistant *S. aureus* (MRSA) became endemic in hospitals in the 1980s [28]. MRSA infections are challenging for antimicrobial therapy and associated with high rates of mortality [29]. Due to enhanced infection control measures, an encouraging decrease in the incidence of invasive MRSA HAIs over the past decade have been observed [28]. Nevertheless in the USA, MRSA continue to be a pathogen of concern [7]. In France, MRSA represents 26% of *S. aureus* infections in the latest nosocomial infection prevalence study [1]. Methicillin susceptible *S. aureus* (MSSA) is therefore responsible for the majority of *S. aureus* HAIs. Both MRSA and MSSA infections need to be considered in the healthcare setting and need to be prevented. *S. aureus* is notably the leading cause of surgical sites infections (SSI) and device-related infections [30]. Huge costs are associated with the management of *S. aureus* HAIs, for example central-line associated bloodstream infections were estimated to cost from $10,000 to $15,000 per episode [28]. Economic model analysis has shown that a vaccine against *S. aureus* will be cost-effective [31,32].

However, developing a *S. aureus* vaccine has proved to be challenging. Firstly, as *S. aureus* is a commensal and a frequent pathogen, immune response pre-exists in human beings before vaccination [33] and may interact with vaccine response. The bacterium is able to evade immune responses [34]. The impact of carriage on vaccine response and the role of vaccine on carriage has not been considered for long time [22]. *S. aureus* HAIs are however endogenous in 80% of cases [27] and so to prevent *S. aureus* HAIs, we could then hypothesize that a vaccine that does not reduce carriage of the bacterium probably would be less effective. Secondly, immune response to *S. aureus* involve not only humoral response as though for long time, but also cellular response [22,35]. The belief that humoral response is crucial in the immune response against *S. aureus* leads to the development of vaccines based mainly on humoral response. This belief is based on an error of analysis of the risk factor of *S. aureus* infections among patients with hypogammaglobulinemia, that was over-estimated [36]. Thirdly, *S. aureus* is a complex pathogen with many virulence factors and a variable expression of antigens [27]. Vaccines targeting only one antigen were, as is now common knowledge, in fact doomed to failure. Then, lack of predictive animal models was highlighted by the absence of correlates of protection between

humans and rabbit or mouse models [22]. Although opsonophago-cytic activity has proved to be a predictive biomarker for murine models of infection, this activity has however not been translated to humans' protection. As a consequence, all the clinical trials using this biomarker failed [36]. All these elements explain, at least in part, the reasons for the failure of the first two *S. aureus* vaccines that reached clinical phases, StaphVAX and V710. For the Pfizer vaccine (SA4Ag), futility was the reason to discontinue the phase IIb [37].

Different vaccines platforms have been evaluated against *S. aureus* which are presented in Table 2.

StaphVAX from NABI biopharmaceuticals, was a vaccine which targeted the capsular polysaccharides 5 and 8 of *S. aureus*, conjugated to the *Pseudomonas* exotoxin A as protein carrier. Two clinical trials were performed in hemodialysis patients. The tolerance was good but the clinical endpoint - the reduction of *S. aureus* bacteremia- was not achieved [38,39]. Consequently, further development of this vaccine was stopped. Beyond the reasons for the failures exposed above, suboptimal vaccine quality and a need to expand the antigen composition of the vaccine were the reasons given by investigators to explain this result. This vaccine had no impact on the nasal carriage as it was observed in an ancillary study [40].

The V710 trial from Merck, studied a vaccine that targeted IsdB, an iron scavenger of *S. aureus.* A randomized clinical trial including more than 8,000 adults scheduled for cardiac surgery was carried out, the primary endpoint was the reduction of *S. aureus* SSI. The trial was prematurely interrupted because of concerns about a 5-fold increase in the mortality rate due to *S. aureus* infections in the vaccine group, associated with a significant number of side effects and a lack of efficacy [41]. These findings raise concern that immune predispositions may adversely impact the safety and efficacy of staphylococcal vaccines. This vaccine also had no impact on *S. aureus* carriage [41].

The Pfizer's SA4Ag was composed of 4 antigens: clumping factor A, a virulence factor that allows *S. aureus* to bind to fibrinogen; CP5; CP8 and the manganese transporter MntC. Three of these antigens had already been tested and were associated with failures [42,43]. Data from phase I/II revealed that the vaccine was well tolerated, and elicited robust humoral response but low cellular response [44], this observation may in part explain the absence of efficacy in clinical trials [37]. The impact of this type of vaccines on *S. aureus* carriage was evaluated in a Phase I trial in Australia evaluating safety and immunogenicity of a non-adjuvanted SA3AG vaccine combining clumping factor A, CP5 and CP8 in healthy adults [45]. In spite of immunogenicity, vaccine did not impact *S. aureus* carriage and acquisition, around 30% of the study participants were *S. aureus* carriers at baseline [45].

A phase I study using as vaccine antigen rAls3p-N (NDV-3, Novadigm Therapeutics), an epitope shared by *Candida* and *S. aureus* was completed and showed humoral (IgG and IgA) and cellular response (TNF and IL17a) [46]. This approach is based on convergent immunity, demonstrating the possibility of cross-kingdom protection since *Candida* and *S. aureus* shared epitopes and have a mucosal distribution [47]. A single-dose of this vaccine was evaluated in a phase II (randomized, double-blind, placebo controlled) trial in 380 US militaries, endpoints were safety, immunogenicity and efficacy [48]. This vaccine candidate seemed to be well tolerated and immunogenic in young adults (median age 20 years), however, the frequency of *S. aureus* oral or nasal acquisition did not differ between vaccine and placebo recipients (25.6% *vs* 29.1%).

A five antigen vaccine developed by GSK (GSK SA5Ag) entered Phase I/II development in 2020, in healthy adults and adults under 50 years of age with history of skin soft tissue infections [49].

STEB-Vax was a recombinant Staphylococcal Enterotoxin B vaccine. Although Phase I results were obtained in 2016 and supported its continued clinical development, we did not identify further clinical trials [50].

IBT-V02 (Integrated Biotherapeutics) targets six SA toxins including the pore-forming toxins alpha hemolysin (Hla), Panton-Valentine leukocidin (PVL), leukocidin AB (LukAB), and the superantigens toxic shock syndrome toxin-1 and staphylococcal enterotoxins A and B. This vaccine will probably enter in clinical development after the demonstration of efficacy in mice to prevent soft and skin tissue infections due to *S. aureus* [51].

rFSAV (Olymvax) is a recombinant vaccine with 5 antigens: the secreted factors α-hemolysin (Hla), staphylococcal enterotoxin B (SEB) and the three surface proteins staphylococcal protein A (SpA), iron surface determinant B N2 domain (IsdB-N2) and manganese transport protein C (MntC) [52]. This vaccine protected mice against lethal *S. aureus* sepsis and pneumonia.

Clostridium difficile vaccines

Clostridium difficile, a Gram-positive, spore-forming bacterium is the leading cause of antibiotic-associated diarrhea and is associated with broad-spectrum antibiotic use, advanced.

age (>65 years), hospitalization, and underlying comorbidities. *C. difficile* has mainly an endogenous origin [53], however cross transmission from hands of HCWs may also occur [54]. In the USA, *C. difficile* infections (CDI) represent the most common pathogen in HAIs [55]. In Europe, *C. difficile* represented the 8th most frequently detected microorganism among HAIs in 2011–2012 [5] and the incidence of CDI in hospitalized individuals was estimated to be 2.9 per 10,000 patient-days in 2016 [56]. In France it represented around 2% of HAIs in 2017 among hospitalized patients

Table 2
Overview of the Staphylococcus aureus vaccine candidates.

Potential Vaccine platforms	Candidates	Company	Phase of clinical development
Recombinant proteins (glycoconjugation)	StaphVax	Nabi pharmaceuticals	Stopped
	V710	Merck	Stopped
	SA4Ag	Pfizer	Stopped in phase IIb
	NDV-3SA5Ag (adjuvanted)	Novadigm therapeutics	Phase II
		GSK	Phase I/II
	STEB-Vax	Integrated Biotherapeutics	Phase I completed
	rFSAV	Olymvax	Phase II
	IBTV02	Integrated Biotherapeutics	Planned
Whole cell vaccines and Live-attenuated vaccination	Lysigin and Startvac (veterinary use)		Veterinary use
Nucleic acid vaccines	No current candidate		
Extracellular vesicles	No current candidate		

[1]. Worldwide outbreaks involving the hyper-virulent strain BI/NAP1/027, have also drawn attention to this pathogen, for which treatment remains challenging. Antimicrobials are often associated with recurrences of the infection and alternatives such as fecal microbiota transplantation have been proposed [57]. The economic burden of CDI, including the costs of complications and recurrence that increase at each subsequent episode, has been estimated to be $4.8 billion annually in the United States [58]. Using a model of transmission, *C. difficile* vaccination appears, in a projected effectiveness study, to be the most desirable strategy in settings or patient groups where levels of broad-spectrum antimicrobial use are high and difficult to reduce [59]. In addition, assuming an incidence of CDI at 5 per 10.000 patient-days, an efficacy ranging from 60 to 90% and a vaccine coverage at 40% of high risk patients, vaccination against *C. difficile* is a cost-effective strategy in a hospital setting [60]. A vaccine against CDI and CDI recurrence may therefore contribute to reduce the burden of HAIs.

Defense against *C. difficile* infection is primarily mediated by the gut microbiota and its perturbation through the use of antibiotics induces significant changes that favor *C. difficile* germination and growth. The vegetative bacterium produces toxins that are responsible for the pathogenesis [61]. Three toxins have been described: toxin A, toxin B or the binary toxin notably released by the strain BI/NAP1/027. While innate immune response is ineffective against these toxins, adaptive immunity is effective and is the base of vaccines in current development [62,63]. Therefore, developed vaccines focus on toxoid preparations of toxin A and toxin B formulated with alum. The vaccine efficacy is correlated with serum neutralizing antibodies against both toxins [62,63].

The preventive *C. difficile* vaccine developed by Sanofi Pasteur, was a toxoid-based vaccine containing formalin-inactivated purified TcdA and TcdB adjuvanted with alum. A phase II successfully conducted allowed to determine the better dose and showed no safety concerns [64]. Three parenteral doses were administered to achieve protective serum antitoxin antibody levels in the targeted population. A phase III (Cdiffense) trial in patients aged 50–85 years at risk of infection, had estimated completion date in October 2019. However in December 2017, this study was stopped after an interim analysis for futility [65]. The results of this phase III trial were published in 2021, and the vaccine candidate was shown ineffective to prevent CDI [66]. CDI incidence was similar in vaccine recipients and placebo group, and close to the reported incidence in the USA. Different hypotheses could be made to explain these results: observed immune response was lower than expected and observed in Phase II trials, a rapid decrease in immune response was observed after vaccination, a lower response to toxin B was also observed. In addition, vaccination might not induce appropriate immune response to effectively neutralize toxins in the intestinal tract [66].

Pfizer is also developing a toxoid-based vaccine using genetically engineered toxoids A and B from a nontoxigenic *C. difficile* host strain adjuvanted with alum [67]. Safety and immunogenicity data were recently published [68]. Two vaccine schedule were evaluated: three doses at Month 0, Month 1 and Month 3, or three dose at Day 1, Day 8 and Day 30. This candidate vaccine seems to be immunogenic in adults aged from 50 to 84 years, and safe. Reactogenicity seems to be higher than expected in adults aged from 50 to 64 years, and lower in adults over 65 years of age. Interestingly, immune response seems to remain stable throughout the study period (12 months) [68]. Three phase III trials are ongoing worldwide and in the USA, one of these trials compare the efficacy of a 2-dose vaccine schedule to a 3-dose vaccine schedule. On the 1st of March 2022, in a press release, Pfizer announced that although the primary endpoint was not reached in the Clover clinical trial, the vaccine had reduced the severity and the duration of CDI [69].

Valneva has completed a phase I and phase II study of a recombinant toxin domain, with or without aluminum hydroxide as an adjuvant (VLA84). Good safety, tolerability, and immunogenicity profiles were seen in both healthy adults and healthy at-risk volunteers aged 65 years and older [70]. Sustained immune response was observed in healthy adults between 18 and 65 years of age, whereas a decrease in toxin A and toxin B IgG levels was observed in the elderly. To our knowledge, there are no ongoing further studies, Valneva is searching for partners. Another vaccine developed by GlaxoSmithKline is currently in Phase I, targeting the F2 antigen of *C. difficile* [71].

These vaccines which induce an immune response against toxins A and B may reduce the rate of *C. difficile* infection but are not likely to prevent bacterium carriage. Colonization is a critical step in *C. difficile* pathogenesis and excreted spores can serve as a significant reservoir of *C. difficile* in healthcare facilities [53,61], so a vaccine preventing or reducing carriage is eagerly awaited [72].

Vaccines against gram-negative bacteria involved in HAIs

Enterobacteriaceae represent up to 38% of HAIs in Europe [5]. In France and in Europe, *E. coli* is the most frequently agent responsible for documented nosocomial infections [1,5] and it is the third agent in the USA [55]. According to the European Centre for Disease Prevention and Control, the rate of *E. coli* resistant to cephalosporins of 3rd generation ranged, in 2020, from 6.6% in the Netherlands to 41.4% in Bulgaria [73]. In Europe, the rate of carbapenem-resistant *Klebsiella pneumoniae* ranged on 2020 from 0.1% in Finland to 66% in Greece [73]. *Pseudomonas aeruginosa* and *Acinetobacter baumanii* are also often documented among HAIs notably in intensive care units (ICU) patients [30]. These pathogens are also frequently resistant to antimicrobials with respectively 31.8% and 81.2% of *P. aeruginosa* and *A. baumanii* isolates non susceptible to carbapenems [5]. As resistance against new antimicrobials is rising, the development of other strategies is warranted [74].

Vaccines against extra-intestinal pathogenic *E. coli* are under development. The ExPEC O-antigen, a component of the surface lipopolysaccharide, is a promising vaccine target [75]. Janssen had developed a 9-valent bioconjugated vaccine with *P. aeruginosa* exoprotein A, currently entering in Phase III [76] in adults aged 60 years and older with a history of urinary tract infection in the past 2 years. Primary endpoint will be occurrence of a first invasive extraintestinal pathogenic *E. coli* disease event with microbiological confirmation in blood, other sterile sites, or urine, caused by 9-valent extraintestinal pathogenic *E. coli* vaccine serotypes. The 4-valent form of this vaccine demonstrated its safety and its immunogenicity in a Phase II trial, including adults (median age 55 years) and 68% of the participants were 50 years and older [75]. Immune response seemed sustained across the time, but a decrease in antibody titers was observed. In addition, vaccination was not associated with changes in gut microbiome.

Different vaccine strategies against *K. pneumoniae* have been investigated: whole cell vaccines and mixed bacterial vaccines, capsular polysaccharides, Outer Membrane Vesicles (containing lipids, cell wall structures, nucleic acids, and toxins), proteins based formulations (outer membrane proteins, toxins, other proteins like siderophores), ribosomal vaccines [77]. A tetravalent bioconjugate vaccine including O antigen-polysaccharides (GSK) is entering in clinical phases with a Phase I/II trial [78]. To our knowledge, it is the unique *K. pneumoniae* currently under clinical development. Mixed bacterial vaccines were already investigated with heterogeneous results [77].

Valneva developed IC43, a vaccine targeting 2 outer membrane proteins OprF and OprI against *P. aeruginosa*. The target population

was critically ill patients. Promising results were observed in phase II with good rate of seroconversion using 2 doses 7 days apart and a 28-day mortality lower in all vaccine groups compared to placebo (statistically significant for the non-adjuvanted vaccine compared with placebo) [79,80]. A phase II/III randomized, placebo-controlled, double-blind study was conducted in 800 mechanically ventilated ICU patients at 52 trial sites in 6 European countries [81]. All-cause mortality at day 28 was similar in placebo and recipient groups, in spite of high immunogenicity. No differences were observed for incidence of *P. aeruginosa* pneumonia or colonization at day 14 and day 90. No differences were observed for incidence of *P. aeruginosa* pneumonia or colonization at day 14 and day 90. Other vaccines are currently evaluated in pre-clinical studies like: a live aroA-aroB attenuated Salmonella vaccine, live-attenuated whole cell vaccines, and vaccines with different antigens the iron acquisition protein Hit, or PA5340 combined with PA3526-MotY, PcrV with CpG oligodeoxynucleotide, or the pilus proteins PilQ and PilA [82]. To our knowledge, no clinical trial is undergoing for these vaccines.

Acinetobacter baumannii was identified by WHO as one of the three antibiotic-resistant bacterial species on its list of global priority pathogens for novel and effective treatment. Vaccines might be useful approaches. Different technologies could be adequate [83]. To date, there is no vaccine in clinical development.

HCWs immunization to reduce the burden of HAI

There are two main reasons to consider HCWs immunization to prevent HAI due to multidrug resistant or difficult to treat microorganisms. First, HCWs are in contact with patients susceptible to communicable diseases, sometimes immunocompromised, highly susceptible to certain pathogens and/or not eligible for vaccinations (like children under 6 months old). The concept of "herd immunity" might be applied in the context of healthcare settings. The risk of infections among susceptible individuals in a population is reduced by the presence and the proximity of immunized persons [84]. Vaccines may have an indirect effect by reducing infectiousness, and consequently protect individuals that remain susceptible [84]. Secondly, HCWs may be at high-risk of MDRO acquisition and may have a direct benefit to vaccination. However, an excess risk of MDRO colonization was not observed in an American study carried out in 400 HCWs and 400 controls, no difference was observed between HCWs who reported caring for MDRO-colonized patients, and HCWs who did not report [85].

Such a strategy will face different difficulties. First, vaccines should have an impact on pathogens carriage in HCWs. Although the primary source of *S. aureus* HAIs is endogenous [27], contacts between patients and HCWs carrying *S. aureus* may facilitate incident colonization in patients [86,87]. HCWs have been reported as a source of healthcare-associated *S. aureus* infections outbreaks [88]. *S. aureus* carriage may concern more than 30% of HCWs [88,89]. To be effective to prevent transmission between HCWs and patients and consequently to reduce the number of HAIs related to exogenous *S. aureus* infections in patients, a vaccine dedicated to HCWs need to have an impact on carriage. Until now, vaccines developed with released results had no impact on nasal carriage [22]. Asymptomatic intestinal carriage of toxigenic *C. difficile* may concern 15% of the general population [90] and this prevalence of carriage was found to be similar in HCWs [91]. We did not identify published outbreaks caused by a strain carried by a HCW. The impact of current vaccines in development on *C. difficile* carriage remains unclear. Moreover, the majority of *C. difficile* transmissions are related to lack of hand hygiene with strains from the patients or vomits [90]. Consequently, the impact of HCWs immunization on the rate of *C. difficile* infections might be limited.

Implementation of an immunization program in HCWs to prevent HAIs presents several difficulties. First, there are no international guideline for HCWs immunization, some vaccines are mandatory in several countries whereas they are only recommended or not recommended at all elsewhere [92]. As in the general population, vaccine hesitancy affects HCWs [93,94]. Fear of side effects, negative experiences with vaccines, considering vaccines as an invention of the pharmaceutical industry, additional doctor's appointment and feeling themselves at low risk of infection were frequently reported as barriers to immunization in HCWs [95,96]. During the COVID-19 pandemic, self-protection was one of the main motivations to get vaccinated in HCWs [97]. Potential acceptance of vaccines used to mainly protect patients is difficult to estimate. Moreover, defining specific populations of HCWs (individuals working in ICU, in contact with immunosuppressed patients, at-risk for severe infections HCWs) is crucial question.

Conclusion

In 2019, the World Health Organization estimated that by 2050, 10 millions of people will die each year from a drug-resistant disease [98]. The development of vaccines against pathogens involved in HAIs may contribute to the response to this global challenge. However, for most of the pathogens involved in HAIs vaccines are not currently available and the development of effective vaccines for *S. aureus* or Gram-negative bacteria remains challenging, for *C. difficile*, the goal of obtaining a preventive vaccine seems to be near. Many questions need to be addressed before completing the availability of vaccines against HAIs. First, a great part of HAIs is caused by commensal pathogens present prior to hospitalization (endogenous infections). Consequently, vaccination of patients during hospitalization comes too late, and immune response could be impaired by pre-existing immunity and tolerance to microbiota [77]. Secondly, definition of the at-risk populations, and anticipation of the at-risk situations (scheduled surgery, immunosuppressive agents, hemodialysis) are crucial. Thirdly, HAI at-risk patients are also patients who have experienced a weak response to vaccines. To circumvent this latter issue, there are two different strategies: vaccination of HCWs, and identification of strategies to enhance vaccine responses in elderly and immunocompromised populations. Vaccination of HCWs may have an impact as observed for vaccination against seasonal influenza. However, in the context of HAIs prevention, the role of HCWs in the acquisition of pathogens by patients should be evident, the vaccine should have an effect on the carriage of the pathogens, and the vaccine should be safe as direct benefit for HCWs is uncertain. Then, an evaluation of the acceptability of these potential vaccines both in patients and HCWs is necessary whereas vaccine acceptance is challenging in community settings. Until preventive vaccines are available, infection control measures continue to be crucial in the prevention of HAIs and should be strengthen. As the spectrum of antimicrobial resistance is not limited to humans, a OneHealth response is necessary, and in parallel to the development of vaccines for humans, development of vaccines for animals remains crucial.

Data statement

We did not provide any original results. This article is a narrative review. We do not have access to the presented data.

CRediT authorship contribution statement

Gagneux-Brunon Amandine: Conceptualization, Writing – original draft. **Julie Gagnaire:** Writing – original draft. **Carole Pelissier:** Writing – review & editing. **Berthelot Philippe:**

Writing – original draft. **Botelho-Nevers Elisabeth:** Conceptualization, Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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